REMARKS

Pending Claims

Claims 35 and 53 are pending in this application. Claim 35 is drawn to an in vitro method for screening substances for new immunosuppressive agents. Claim 53 is drawn to an in vitro method for screening substances for new immunoenhancing agents.

The Office Action

The Examiner acknowledged Applicant's election of Group V, claims 35 and 53, in response to a restriction requirement. The Examiner stated that election was made without traverse.

Claims 1-24 and 36-52 have been cancelled, as being drawn to non-elected inventions. Claims 35 and 53 are currently under consideration.

The Examiner denied the priority claim to the provisional application 60/031,338, 08/894.251, PCT/US97/21463, and 09/569,956, because the association of PTTG with T lymphocytes, and the changes of PTTG mRNA in response to immunosuppressive agents, were not disclosed in the cited applications. The priority date of the instant application was established as a filing date of the instant application, namely October 13, 2000.

The disclosure was objected to because of purported informalities of the brief description of the drawings. Specifically, the Examiner objected to Figures 9-13 because it was unclear what the multiple columns in each figure represented, e.g., a different type of cell or a duplication of the same type of cell.

In response, Applicant has amended the description of Figures 9-13 in the specification, for greater clarity.

Applicant has also amended the specification at page 83, line 2, by correcting an obvious typographical error in the spelling of the word "mixture," and at page 83, line 5, by hyphenating the expression "T-cells."

Applicant has also amended the specification at page 84, line 10, by correcting an obvious typographical error in the spelling of the word "chromatid."

The Examiner objected to Claim 35, because the claim recitation of "Pituitary Tumor Transforming Gene", represented by the the acronym "PTTG", was not spelled out the first time it appeared in the claims. In response, Applicant has amended Claim 35, at lines 6-7, to spell out "Pituitary Tumor Transforming Gene (*PTTG*)."

Claims 35 and 53 were objected to because "a conjunction word is missing before the last phrase of the claims." In response, Applicant has overcome this objection by amending Claims 35 and 53, respectively to insert the word "whereby" at the beginning of the last phrases of the claims.

In addition, Applicant has amended Claim 35, at line 9 to correct an obvious typographical error in the spelling of the word "immunosuppressive."

Applicant has also amended Claim 35, at line 7, and Claim 53, at line 5, by inserting "T-" before the word "lymphocyte," merely to better conform with antecedent basis, for the sake of greater clarity.

It is believed that no new matter is added by any of the above-noted amendments.

No claims were allowed.

The Examiner presented the following grounds of rejection.

I. Rejections based on 35 U.S.C. § 112, first paragraph.

The Examiner rejected Claims 35 and 53 for the following reasons:

...The specification teaches that PTTG mRNA and protein expressions are cell cycle-dependent and peak at G2/M phase, that PTTG mRNA expression could be detected in many different tumor cells (table 16), than when resting human T cells were treated with a T-cell mitogent, e.g. anit-CD3 antibody, T cells began to proliferate and sequentially exntered S phase and G2/M phase. Parallel to this proliferation is the PTTG mRNA expression, which was dramatically increased for more than 30 times from the levels in the resting T cells (fig. 5). When the activated T cells were treated with various agents, such as immunosuppressive hydrocortisone, cyclosporine A (CPA) and TGF-β1, or antibiotics aphidicolin, or antineoplastics necodazoloe, the expression of PTTG mRNA was suppressed to various degree, with the cycloporine A being the most effective. However, the experimentation was conducted only in T cells, normal or leukemic. Therefore, when the data were considered with what is known in the art, a doubt is raised on whether the changes of PTTG mRNA level in T cells in response to various agents are immunological related or cell cycle related.

Applicant disagrees with this basis of rejection, because, in general, when T-cells are "activated", the T-cells are "proliferative". It is believed that these two terms describe the same state in T-cells, and a distinction between "T-cell activation" and "T-cell proliferation" is merely semantic; whether changes in PTTG mRNA level in T cells are stated as "immunologically-related" or "cell cycle-related," both terms indicate that the PTTG mRNA level (an indicator) in the T cell has changed in response to a mitogen, and, as such, the mitogen has "activated" the T-cell. Such activation of the T-cell typically results in the proliferation of the T-cell. Consequently, Applicant respectfully requests that the Examiner withdraw the rejection of Claims 35 and 53 on this ground.

The Examiner also stated that:

> **Claims are drawn to detecting a change in the expression level of PTTG protein. However, in the working examples of the specification, the changes were detected and demonstrated by its mRNA expression, since such mRNA changes may not necessarily [be] reflected in the expression of PTTG protein, the specification fails to provide sufficient guidance with regard whether the changes could be detected at the protein level, the expression patterns of PTTG protein in response to the recited agents, the sensitivities of detection methods, thus, fails to support the full scope of the claims.**

Applicant disagrees. The general knowledge of the art teaches a correlation between PTTG mRNA expression and PTTG protein expression. Skilled artisans interchangeably use both Western Blot analysis (detecting PTTG proteins) as well as Northern Blot analysis (detecting PTTG RNA) to detect PTTG expression. For example, Applicant submits herewith Exhibit A: Zhang *et al.*, Molecular Endocrinology 13(1):156-166 (1999); Exhibit B: Heaney *et al.*, Nature Medicine, 5(11):1317-1321(1999), Exhibit C: Heaney *et al.*, The Lancet, 355(9205):716-719 (Feb. 2000), all of which are pre-filing date references previously cited in Applicant's Information Disclosure Statement, mailed January 30, 2001. These three references describe the use of *both* Western Blot (as specific PTTG protein detection means) and Northern Blot (as specific *PTTG* mRNA detection means) to detect PTTG expression. There being a correlation shown in the art between expression of *PTTG* as detected by measuring *PTTG* mRNA or PTTG protein, the skilled artisan would be able to detect *PTTG* expression, in accordance with the claimed invention, by either means.

Consequently, Applicant respectfully requests that the Examiner withdraw the rejection of Claims 35 and 53 on this ground.

II. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected Claims 35 and 53 for the following reason:

...The claims are vague and indefinite because the methods comprising a step of detecting a change in the expression level of PTTG in the T-lymphocytes, however, it does not recite a positive step that clearly defines the means for detection, thus, the metes and bounds of the claims are unclear. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will be set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, Ex parte Erlich, 3 USPQ2d 1011 at 6.

Applicant disagrees with the Examiner's assertion that the patent statute requires the recitation of a particular means for detection. Applicant submits that "detecting a change in the expression level of Pituitary Tumor Transforming Gene (*PTTG*) in the T-lymphocytes...," as recited in Claims 35 and 53, is in itself "a positive, active step." The specification and the knowledge in the art, together, teach a variety of techniques for "detecting" that would be known and available to the skilled artisan, including procedures involving nucleic acid amplification and/or hybridization of specific probes (e.g., specification, at page 44, line 28 through page 48, line 29, citing, *inter alia*, RT-PCR, TMA, RT-LCR, Northern analysis, FISH), or the use of immunoreagents (e.g., specification, at page 52, lines 17-24, citing, *inter alia*, ELISA, immunofluorescence assay [IFA], Pandex microfluorimetric assay, agglutination assays, flow cytometry, serum diagnostic assays and immunohistochemical staining procedures). Thus, it would be clear to the skilled artisan that any suitable detection technique could be chosen for use in detecting the expression level of PTTG.

In view of the disclosures of the specification as originally filed and the general knowledge in the art, it would be unduly limiting to recite only one particular detection method in Claims 35 and 53.

Consequently, Applicant respectfully requests that the Examiner withdraw the rejection of Claims 35 and 53 on this ground.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

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